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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,387	05/21/1999	ALAN SOLOMON	UNIE-014/01US 306680-2015	7724

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COOLEY GODWARD KRONISH LLP
ATTN: Patent Group
Suite 1100
777 - 6th Street, NW
WASHINGTON, DC 20001

EXAMINER	
EMCH, GREGORY S	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,387	SOLOMON ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,28 and 30-50* is/are pending in the application.

4a) Of the above claim(s) *28 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,30-35 and 37-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The response filed on 07 August 2008 has been received and entered in full. No amendments to claims were submitted in said reply. Claims 24, 28 and 30-50 are pending in the instant application.

Claims 28 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in the reply filed on 04 February 2002.

Claims 24, 30-35 and 37-50 are under examination in the instant office action.

Withdrawn Rejections

The rejection of claim 31 under 35 U.S.C. 102(b) as being anticipated by Konig et al. (WO 96/25435) is withdrawn in view of applicants' argument that the reference does not teach a human antibody.

Declaration under 37 CFR § 1.132

The declaration under 37 CFR § 1.132 filed on 07 August 2008, i.e., the declaration of Mr. Stephen Wood, is insufficient to overcome the rejection of claims 24, 30, 35, 39-46, 48 and 49 under 35 U.S.C. 102(b) as being anticipated by Konig et al. (WO 96/25435) as set forth in the last Office action. The declaration is also insufficient

to overcome the rejection of claims 24, 30-35 and 37-49 under 35 U.S.C. 102(b) as being anticipated by Becker et al. (EP 613007) and the rejection of claim 50 under 35 U.S.C. 103(a) as being unpatentable over by Konig et al (WO 96/25435).

Item 3 of the declaration states that experiments were performed under the supervision of Mr. Wood, wherein binding of monoclonal antibody (mAb) 369.2B (the antibody disclosed the cited document WO 96/25435) to Aβ was compared to control antibody 2.1 chimera (mAb 2.1). Item 4 states that in an *in vitro* experiment, which appears to be an Enzyme Linked Immunosorbant Assay (ELISA), mAb 369.2B does not bind to Aβ1-40 fibrils or monomers, while 2.1 chimera does bind. Item 5 states that in the same *in vitro* assay, mAb 369.2B exhibits weaker binding to Aβ1-42 when compared to 2.1 chimera.

Regarding items 4 and 5, the prior art of record, i.e. the Konig et al. reference, teaches that mAb 369.2B is a C-terminal antibody that binds to Aβ1-42, but does not bind to Aβ1-40 (see Examples 6 and 7, pp.22-26). Consistent with the disclosure of the Konig et al. reference, Exhibit 1B of the declaration shows that mAb 369.2B binds to A-beta 1-42 fibrils, and Exhibit 2B shows that mAb 369.2B binds to A-beta 1-42 monomers. Thus, the experiments outlined in items 4 and 5 are expected from the teachings of the prior art, and the fact that mAb 2.1 has allegedly better binding than does mAb 369.2B does not disprove the therapeutic efficacy of the mAb 369.2B *in vivo* in humans with Alzheimer's disease.

Item 6 of the declaration states that immunohistochemistry was performed to demonstrate whether mAB 369.2B bound to amyloid plaques in unfixed brain tissue

sections from an 18 month-old Tg2576 mouse (a transgenic mouse model of Alzheimer's disease). The declaration asserts that the data show that there is little binding of mAb 369.2B to plaques in the brain tissue when compared to mAb 2.1. The declaration asserts that these data confirm the results described in items 4 and 5, i.e. that mAb 369.2B has low binding affinity for amyloid fibrils. The declaration asserts that the low level binding exhibited by mAb 369.2b is not sufficient to opsonize amyloid fibrils and induce removal of amyloid deposits *in vivo*.

This is not found persuasive for the following reasons. The Konig et al. reference teaches that mAb 369.2b binds to human Aβ1-42 peptide in an *in vitro* immunoprecipitation/scintillation assay (non-solid phase) and an ELISA (solid phase) (see Example 6, pp.22-24). The Konig et al. reference also teaches results from immunohistochemical studies performed in tissue sections from the brain of a 76 year old female patient with Alzheimer's disease. It is taught that mAb 369.2B was "an excellent antibody (at 1/10,000 dilution) to specifically label amyloid plaque cores, diffuse as well as fibrillar amyloid deposits and vascular amyloid deposits." and that staining was abolished in the presence of competing Aβ1-42 peptide (see Example 7, pp.24-26). Therefore, the results outlined in the Konig et al. reference are in direct contradiction with the results outlined in the declaration. The declaration asserts that mAb 369.2b has a low level of binding in amyloid fibrils from tissues sections of an 18 month-old Tg2576 mouse, whereas the Konig et al. reference teaches that mAb 369.2b has a high level of binding in amyloid fibrils from the brain of a 76 year old human with Alzheimer's disease. Since the data set forth in the declaration is from a mouse model

of Alzheimer's disease and the data set forth in the Konig et al. reference is from an actual patient with Alzheimer's disease, the data set forth in the Konig et al. reference is given greater weight for predicting the efficacy of mAb 369.2b in treatment of Alzheimer's disease.

Item 7 states that an *ex vivo* phagocytosis assay was used as an efficacy test for the antibodies by evaluating an antibody's capacity to induce phagocytosis of amyloid plaques. The declaration asserts that it has been shown previously that this phagocytosis assay is the best available predictor of *in vivo* antibody efficacy (reduction of plaque burden) in mouse models of Alzheimer's disease and cites Exhibit 6 (Bard et al., PNAS, 2003) in support of this assertion. Item 8 states that cell binding and tissue binding assays were performed by increasing amounts of the indicated antibodies incubated with unfixed brain sections from a 19 month-old Tg2576 mouse and microglial IC21 cells (a phagocytic cell-line). The declaration asserts that increasing the concentration of mAb 2.1 resulted in a concentration-dependent increase in phagocytosis and that phagocytic efficacies of other Aβ binding antibodies, including mAb 369.2b, were substantially reduced when compared to mAb 2.1. The declaration asserts that the minimal level of phagocytic activity induced by mAb 369.2b would not be predicted to remove amyloid deposits *in vivo*.

This is not found persuasive for the reasons set forth above. The results from the *in vitro* phagocytosis assay were also obtained from the Tg2576 mouse and not from a patient with Alzheimer's disease. Given that the data from the phagocytosis assay was obtained from the same tissue source, it is not surprising that the results are

consistent with the binding data also disclosed in the declaration. Again, since the data set forth in the declaration is from a mouse model of Alzheimer's disease and the data set forth in the Konig et al. reference is from an actual patient with Alzheimer's disease, the data set forth in the Konig et al. reference is given greater weight for predicting the efficacy of mAb 369.2b in treatment of Alzheimer's disease. Although Exhibit 6 alleges that the phagocytosis assay is the best available predictor of *in vivo* antibody efficacy for mouse models of Alzheimer's disease, this assay is not necessarily the best available predictor of *in vivo* antibody efficacy for actual patients with Alzheimer's disease, given the disparity between the results set forth in the Konig et al. reference and those set forth in the instant specification. Regardless, none of the claims recite any particular dose. The claims (e.g. independent claims 24 and 46) only recite "in an amount effective to remove amyloid deposits." The declaration filed by applicants provides evidence that the 369.2B antibody is in fact effective to remove plaques. Note that Exhibit 4 shows that mAB 369.2B is better than control in the phagocytosis assay, i.e. the antibody does remove some plaques. Similarly, as stated above, Exhibit 1B of the declaration shows that mAb 369.2B binds to A-beta 1-42 fibrils, and Exhibit 2B shows that mAb 369.2B binds to A-beta 1-42 monomers. While the antibody may have different binding efficiency/phagocytosis ability than the 2.1 chimera, the declaration filed by applicants provides evidence that the prior art antibody binds and opsonizes. Given the breadth of the claims, which recite only "an amount effective to remove" deposits, the teachings of the prior art that there is an effective amount used in the

treatment methods, and the evidence provided by applicants, the claims are anticipated by the prior art of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 24, 30, 35, 39-46, 48 and 49 under 35 U.S.C. 102(b) as being anticipated by Konig et al. (WO 96/25435) is maintained for reasons of record and as set forth below.

In the response filed on 07 August 2008, applicants assert that the Konig et al. reference does not teach each and every limitation of the claimed invention. Applicants assert that the Bard et al., PNAS, 2003 reference (referred to Exhibit A here and as Exhibit 6 in the declaration under 37 CFR § 1.132) states that "[w]e have shown previously that not all antibodies against Aβ can trigger plaque clearance *in vivo*." Applicants assert that Bard further states that C-terminal antibodies were inactive and were not effective in reducing plaques *in vivo*. Thus, applicants assert that since the 369.2B antibody is a member of the Aβ C-terminal binding class of antibodies, there is strong evidence that 369.2B will not be effective in reducing plaques *in vivo*. Applicants repeat the assertions set forth in the declaration filed under 37 CFR § 1.132 as allegedly providing further support that mAb 369.2B will not be effective in reducing plaques *in*

vivo. Applicants further assert that there is no mention of using human antibodies in the entire specification of the Konig et al. reference and that the reference cannot anticipate claim 31 for this added reason.

Applicants' arguments have been fully considered and are not found persuasive. With regards to the declaration under 37 CFR § 1.132 (the Wood declaration), as set forth above, the declaration provides evidence that mAb 369.2B is effective to remove plaques. None of the claims recite any particular dose. The claims (e.g. independent claims 24 and 46) only recite "in an amount effective to remove amyloid deposits." Exhibit 1B of the declaration shows that mAb 369.2B binds to A-beta 1-42 fibrils, Exhibit 2B shows that mAb 369.2B binds to A-beta 1-42 monomers and Exhibit 4 shows that mAB 369.2B is better than control in the phagocytosis assay, i.e. the antibody does remove plaques. While mAb 369.2B may have different binding efficiency/phagocytosis ability than the 2.1 chimera, the declaration filed by applicants provides evidence that the prior art antibody binds and opsonizes. Given the breadth of the claims, which recite only "an amount effective to remove" deposits, the teachings of the Konig et al. reference that there is an effective amount used in the treatment methods, and the evidence provided by applicants, the claims are anticipated by the prior art of record.

With regards to the Bard et al. reference, said reference does not teach that all C-terminal Aβ antibodies are ineffective at triggering plaque clearance *in vivo*. Again, that specific antibodies noted in other prior art fail to elicit the desired removal of amyloid would in fact call into question the enablement of the broadly claimed current method, as the instant claims do not recite *any* specific antibody epitope and thus

encompass *any* antibody or immunoglobulin polypeptide. As set forth previously, page 5, lines 1-3 of the instant specification states that "[U]pon the binding or adhering of such immunoglobulin polypeptides to undesired deposits of amyloid fibrils, the latter are believed to be opsonized." At page 12, lines 1-5, the instant specification defines "opsonize" as "the binding of an immunoglobulin polypeptide to a particular target, particularly epitopes found on deposits of amyloid fibrils, such that the antibody and targets together are recognized as "foreign" by the host's cellular immune system. In other words, the binding of the immunoglobulin of the present invention enhances the phagocytization of the amyloid fibrils." Thus, as defined by applicants' own disclosure, there would be no mechanistic difference between administration of the β-amyloid specific monoclonal antibody disclosed by Konig et al. and the instantly claimed antibodies. A prior art reference is not required to teach the mechanism of action in order to meet the requirements of either anticipation or enablement. As both Konig's therapeutic method and the currently claimed method provide for the administration of the same antibodies to the same patient population for the same purpose, the mechanism of removal of amyloid deposits would be inherently expected. The Konig et al. disclosure does not lack any element provided by the claims of the instant application, i.e., the instantly claimed method requires no more than is taught by the Konig et al. reference.

The rejection of claims 24, 30-35 and 37-49 under 35 U.S.C. 102(b) as being anticipated by Becker et al. (EP 613007) is maintained for reasons of record and as set forth below.

In the response filed on 07 August 2008, applicants assert that the Becker et al. reference does not provide an enabling disclosure. Applicants argue that the artisan would have to perform undue experimentation to create and select an antibody to administer to a patient to remove amyloid deposits *in vivo*. Applicants assert that there is no guidance in Becker for one of skill in the art to determine whether an antibody would opsonize the amyloid deposits, as required by the presently claimed invention. Applicants assert that they have submitted evidence that shows that not all antibodies against Aβ opsonize Aβ plaques. Applicants assert that as discussed above, applicants have submitted Bard (Exhibit A) which states "[w]e have shown previously that not all antibodies against Aβ can trigger plaque clearance *in vivo*." Applicants assert that Bard further states that C-terminal antibodies were inactive and were not effective in reducing plaque *in vivo*. Thus, applicants assert that not all antibodies inherently result in the opsonization of amyloid deposits as currently claimed. Applicants repeat the assertions set forth in the Wood declaration as allegedly providing further support that mAb 369.2B will not be effective in reducing plaques *in vivo*.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above regarding the Wood declaration, given the breadth of the claims, which recite only "an amount effective to remove" deposits, the teachings of the Becker et al. reference that there is an effective amount used in the treatment methods, and the

evidence provided by applicants (i.e. that mAb 369.2B binds A-beta 1-42 fibrils and monomers and has phagocytic activity), the claims are anticipated by the prior art of record. In addition, the Bard et al. reference does not teach that all C-terminal Aβ antibodies are ineffective at triggering trigger plaque clearance *in vivo*. That specific antibodies noted in other prior art references fail to elicit the desired removal of amyloid would in fact call into question the enablement of the broadly claimed current method, as the instant claims do not recite *any* specific antibody epitope and thus encompass *any* antibody or immunoglobulin polypeptide. The Becker et al. disclosure does not lack any element provided by the claims of the instant application, i.e., the instantly claimed method requires no more than is taught by the Becker et al. reference.

As set forth previously, there was an effective amyloid model to show that amyloid masses could be removed by an antibody *in vivo* (see for example, Kowall et al., cited previously). Thus, given the *in vitro* guidance presented by the Becker et al. reference and the state of the prior art, it is well within the skill of the artisan to determine administrable amounts of the antibody sufficient to effect the desired response of binding to β-amyloid, inhibiting neurotoxicity and thus providing treatment. It is noted that working examples are not required for anticipation. The question of anticipation here is whether or not the methods are the same or different. Applicants' claims are directed to a method of removing amyloid deposits in a patient comprising administering an antibody or immunoglobulin polypeptide that opsonizes an amyloid fibril and induces removal of amyloid deposits. Alzheimer's disease is a neurodegenerative disorder characterized by the abnormal deposition of protein

aggregates composed of neurofibrillary tangles and amyloid plaque cores (see Becker, column 1, lines 1-10). Becker also teaches that β-amyloid protein that adopts a β-sheet conformation (which conformation is known to form amyloid fibrils and subsequently aggregate into amyloid deposits) is particularly neurotoxic to neurons, and teaches that antibodies specific for β-amyloid peptides of the β-sheet conformation are useful for inhibiting the neurotoxicity of these peptides (see column 5, lines 27-50). Becker additionally teaches the therapeutic use of such antibodies for the treatment of human patients with Alzheimer's disease (column 7, 39-52). The instant claims evidence that the claimed antibodies are reactive with Alzheimer's Aβ protein (claim 41). Thus, both Becker's therapeutic method and the currently claimed method provide for the administration of the same antibodies to the same patient population for the same purpose. Applicants' attention is directed to MPEP § 2121(III) which states that a prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." *Impax Labs. Inc. v. Aventis Pharm.Inc.,* 468 F.3d 1366, 1383, 81 USPQ2d 1001, 1013 (Fed. Cir. 2006). See also MPEP § 2122. Accordingly, the instant rejection of claims 24, 30-35 and 37-49 is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claim 50 under 35 U.S.C. 103(a) as being unpatentable over by Konig et al (WO 96/25435) is maintained for reasons of record and as set forth below.

In the response filed on 07 August 2008, applicants assert that claim 50 is dependent on claim 24, which requires that an antibody is administered to a patient remove amyloid deposits via opsonization. Applicants assert that as stated above, Konig does not disclose an antibody that will remove amyloid deposits *in vivo*, as evidenced by the Wood Declaration. Thus, applicants assert that Kong cannot render claim 50 as obvious.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above, the rejection of independent claim 24 under 35 U.S.C. 102(b) as being anticipated by Konig et al. is deemed proper; therefore, the instant rejection of dependent claim 50 is also deemed proper. Further, the Wood Declaration is insufficient to overcome the instant rejection as set forth above. It is noted that applicants did not traverse the rejection of the specific limitation of claim 50.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
21 December 2008

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
December 22, 2008